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Research Article

One year on glatiramer acetate. Preliminary report on disease activity and disability evolution

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Abstract. Glatiramer acetate for relapsing-remitting multiple sclerosis has already a long history, even if the drug still lacks a precise mechanism of action, and the performed research raised some controversies. Still, the overall clinical effect of the drug is generally thought as beneficial. Our goal was to apply a combined battery of clinical assessment methods, to evaluate the impact of chronic glatiramer acetate treatment on disease activity and disability evolution. This preliminary report shows a beneficial effect of the drug on the relapse rate and on the score of the Expanded Disability Status Scale after one year of continuous treatment, versus non-treated subjects.

Key Words: Glatiramer acetate, relapse, EDSS, multiple sclerosis.

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Introduction

Multiple sclerosis is a devastating demyelinating disease of young adults, which gradually leads to severe disability and finally exitus. Its perfidious character is uncontrolled to this point by any of the existing medications, either the steroids for the relapses, or the various disease modifying drugs. Furthermore, even if these drugs are alleviating severity and are reducing the frequency of relapses in case of relapsing-remitting multiple sclerosis (RRMS), the lack of efficiency is quasi-total in case of the progressive clinical forms.

One of the frequently used disease modifying drugs is glatiramer acetate (GA), a peculiar polymer of four aminoacids, which apparently shares various, still controversial mechanisms – modulating the immune response, mimicking proteins of the CNS, enhancing neuroprotection, etc (Aharoni 2012) – and which presents a diverging impact on the evolutivity of the relapsing-remitting multiple sclerosis. In case of paraclinical evaluation of the diseased, follow-up results cannot entirely seen as favorable, although batteries of neurophysiological (Maier *et al* 2006) and imagery (Cadavid *et al* 2009) tests were performed in different studies. Sometimes technical limits are not permitting a quantifiable response evaluation (Zivadinov *et al* 2012). Despite these, one can observe an intriguing fact: the clinical evolution of the patients is better under the treatment, as mentioned before, somehow in disjunction with the instrumental investigations (Khana *et al* 2001), (Johnson 2012) .

In order to objectively assess the clinical evolution, different measures of quantification were needed (Noseworthy 1994). Annual relapse rate gives a good measure of disease activity, but it lacks information about disability. Kurtzke's Expanded Disability Status Scale was proposed as a measure for the latter, and it is still the most widely used severity scale, used also for clinical trials, although standardization problems are signaled (Hobart *et al* 2000). Still, the EDSS is not standing out for its fine differential evaluation method of motor disability, and it virtually lacks cognitive evaluation (Hoogervorst *et al* 2003). To overcome these aspects, another scale was proposed and developed, the Multiple Sclerosis Functional Composite (MSFC) (Fischer *et al* 1999). It covers three dimensions – the timed 25 foot walk test assesses the lower limb disability, the 9-hole peg test is administered to evaluate upper extremity disability and finally the paced auditory serial addition test gives information about cognition, more precisely about auditory information processing and calculation ability (Rudick *et al* 2002) . It seems, to this point, that the MSFC is the most sensitive scale of disability evaluation in MS, and it is the most frequently used in clinical trials (Ozakbas *et al* 2004). Still, in completion of the cognitive assessment, other tests are also available, as The Montreal Cognitive Assessment (MoCA). The latter is considered a rapid test used to investigate different cognitive domains, as attention, memory, language, executive functions, thinking etc. (Krupp *et al* 2011) .

All mentioned scales and measures of activity and progression were applied to our study group; this preliminary report presents only part of these, evaluation, comparison and statistics is ongoing for the others.

Materials and method

Thirty-seven subjects with relapsing-remitting multiple sclerosis were included. Informed consent was signed by all participants,

and the study was approved by the ethics committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca. Demographic data is shown in table 1.

Table 1. Demographic data – age and sex

		GA	NT
Age		36.67 ± 2.15	37.36 ± 2.05
Sex	M	28.57%	28.57%
	F	71.43%	71.43%

After inclusion, two subgroups were formed; one referred further as GA (n=23), under glatiramer acetate (20 mg/s.c. for one year), and another without treatment, named NT (n=14).
Both groups were evaluated for annual relapse rate and EDSS, at inclusion, marked as GA I or NT I, and after one year of follow-up, marked as GA II and NT II.
Statistical analysis was performed after normality of the study groups was tested with the Kolmogorov-Smirnov test. Both sample size and distribution led us to the use of Kruskal-Wallis test for independent samples, followed by Mann-Whitney U test or the Wilcoxon signed rank test, using SPSS version 17. Threshold for significance was $p<0.05$.

Results

Kolmogorov-Smirnov test revealed that number of relapses lacks normal distribution (not shown), and, as a consequence we've applied non-parametric tests.
A non-significant Kruskal-Wallis test revealed tendencies in difference for relapse rate between the four sets of data, corresponding to the two groups at inclusion and at follow-up (p=0.19). Distribution might be more suggestive by consulting graphic 1.

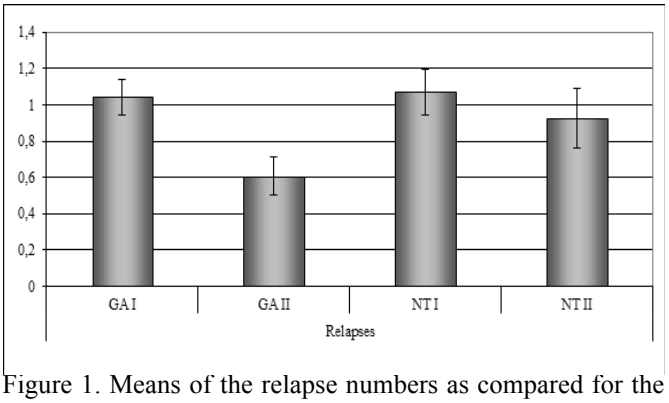

Figure 1. Means of the relapse numbers as compared for the treated and non-treated groups: values being compared are the one-year relapse history prior to enrolment, and the one year after inclusion

Next, we've tested in a paired manner, by applying the Wilcoxon test, if there's a notable difference between the datasets at inclusion and follow-up for the two groups. The nontreated group showed no statistically significant difference, but this was not the case for the GA treated subjects: there was a highly significant (p=0.008) difference between the inclusion and follow-up data, the relapse rate under treatment being lower.
To complete the statistical assessment of the datasets, we've tested also if there were significant differences between the startup measures for the two patient groups: there were no significant differences at inclusion p=0.862, Mann-Whitney U test, nor at follow-up, p=0.118, for the same test.
Kolmogorov-Smirnov test was implemented first also for the EDSS, and revealed normal distribution (not shown), but still, number of participants being fairly low, we've applied non-parametric tests.
As a first step we've applied here also the Kruskal-Wallis test, to validate, if present, between group differences. There was no significant global difference (p=0.524).

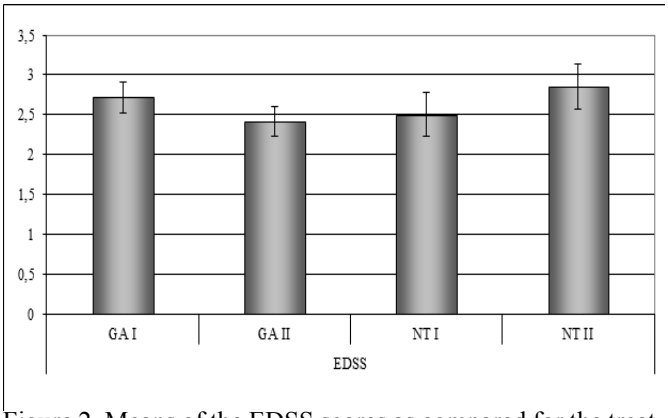

Figure 2. Means of the EDSS scores as compared for the treated and non-treated groups: values being compared are at enrolment, and at the one year follow-up evaluation

Testing continued with the paired comparison of the starting and follow-up datasets for both groups. There were significant differences for both groups (pGAIvsGAII=0.003, pNTIvsNTII=0.008), GA treatment reduces the EDSS score; non-treated patients showed an increase.
The Mann-Whitney tests applied to test the difference between the enrolment and follow-up datasets of the two groups were not significant (pGAIvsNTI=0.515, pGAIIvsNTII=0.215).

Discussion

As we've mentioned in the introduction, several studies found that glatiramer acetate has a statistically significant role on clinical evolution in relapsing-remitting multiple sclerosis. Gradually the drug proved its role of being a feasible therapeutical option for RRMS, despite the questions still unanswered regarding the mechanism of action.
Relapse number and EDSS score, as measures of the therapeutical impact for disease modifying drugs were beneficially influenced by chronic glatiramer acetate treatment in several studies, even to a degree of delaying the diagnosis of clinically definite multiple sclerosis (Comi *et al* 2008) .
Relapse rate shows a significant reduction in our research too, in accordance with other studies, (Martinelli Boneschi *et al* 2003). Still, one remark is suitable here, differences are slight, even if significant, requiring extension of the sample number.
The same fact is observed also for the EDSS score, which shows a favorable evolution under glatiramer acetate treatment, disability is not progressing, there's even an overall, significant reduction of the EDSS score, reported by other studies also, (La Mantia *et al* 2010). We might comment here that the follow-up period was probably too short; we are intending to extend both the evaluation period, and the used assessment measures: MSFC and MoCA, as mentioned in the introduction, to possibly enhance

our results by demonstrating the beneficial effects of GA also on cognitive dysfunction and fine motor function.

Conclusion

Glatiramer acetate significantly improves both relapse frequency and EDSS in relapsing-remitting multiple sclerosis. Further, ongoing study is needed to assess if the medication acts in the same manner on cognitive dysfunction and fine motor function.

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